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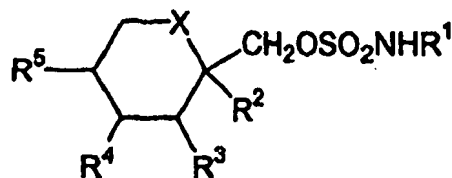
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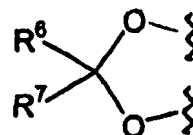
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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL FOR THE TREATMENT OF DEPRESSION



(I)



(II)

(57) Abstract: Anticonvulsant derivatives of formula (I) for the treating depression as monotherapy or combination therapy are disclosed. Wherein X is CH₂ or oxygen; R¹ is hydrogen or alkyl; and R², R³, R⁴ and R⁵ are independently hydrogen or lower alkyl and, when X is CH₂, R⁴ and R⁵ may be alkene groups joined to form a benzene ring and, when X is oxygen, R² and R³ and/or R⁴ and R⁵ together may be a methylenedioxy group of the following formula (II): wherein R⁶ and R⁷ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

ANTICONVULSANT DERIVATIVES USEFUL FOR THE TREATMENT OF DEPRESSION

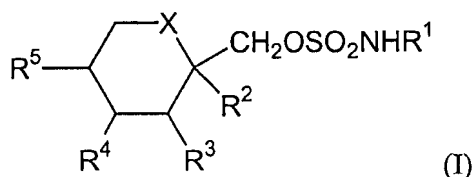
CROSS REFERENCE TO RELATED APPLICATIONS

- 5 This application claims priority from United States provisional application Serial No. 60/222,489 file August 02, 2000, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

- 10 The present invention is directed to anticonvulsant derivatives useful in the treatment of depression, specifically unipolar depression, treatment-refractory depression, resistant depression, anxious depression and dysthymia. The present invention is further directed to the treatment of depression comprising administration of one or more anticonvulsant derivatives in combination with one or more compounds
15 selected from mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitors, natural products, dietary supplements, neuropeptides, compounds targeting neuropeptide receptors or hormones.

- 20 Compounds of Formula I:



- are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (MARYANOFF, B.E, NORTEY, S.O., GARDOCKI, J.F., SHANK, R.P. AND DODGSON, S.P. *J. Med. Chem.* **1987**, 30, 880-887;
25 MARYANOFF, B.E., COSTANZO, M.J., SHANK, R.P., SCHUPSKY, J.J., ORTEGON, M.E., AND VAUGHT J.L. *Bioorg. Med. Chem. Lett.* **1993**, 3, 2653-2656; SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., MARYANOFF, B.E. *Epilepsia* **1994**, 35, 450-460; MARYANOFF BE, COSTANZO MJ, NORTEY SO, GRECO MN,
30 SHANK RP, SCHUPSKY JJ, ORTEGON MP, VAUGHT JL. *J. Med. Chem.* **1998**, 41, 1315-1343). These compounds are covered by three US Patents: No.4,513,006,

No.5,242,942, and No.5,384,327. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate, known as topiramate, has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* **1995**, *36* (S4), 33; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* **1995**, *36* (S4), 33; T.A. GLAUSER, *Epilepsia* **1999**, *40* (S5), S71-80; R.C. SACHDEO, Clin. Pharmacokinet. **1998**, *34*, 335-346), and is currently marketed for the treatment of seizures in patients with simple and complex partial epilepsy and seizures in patients with primary or secondary generalized seizures in the United States, Europe and most other markets throughout the world.

Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* **1994**, *35*, 450-460). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. Topiramate was also found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, *Eur. J. Pharmacol.* **1994**, *254*, 83-89), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, *Epilepsy Res.* **1996**, *24*, 73-77).

Compounds of formula I have further been found to be effective in the treatment of manic depressive bipolar disorder (Shank, US Patent 5,753, 693).

Tollefson et al in WIPO Publication WO99/62522 disclose a method for the treatment of bipolar disease, bipolar depression or unipolar depression comprising administration of an atypical antipsychotic in combination with a compound selected from the group consisting of serotonin reuptake inhibitors, anticonvulsants and lithium.

Unipolar depression is defined as depressed mood on a daily basis for a minimum duration of two weeks. An episode may be characterized by sadness, indifference or apathy, or irritability and is usually associated with a change in a number of neurovegetative functions, including sleep patterns, appetite and body weight, motor agitation or retardation, fatigue, impairment in concentration and decision making, feelings of shame or guilt, and thoughts of death or dying (*Harrison's Principles of Internal Medicine*, 2000). The criteria for a major depressive episode includes five or more symptoms present during the same 2-week period, where this represents a change from previous functioning; and where at least one of the symptoms is either depressed mood or loss of interest or pleasure. Symptoms of a depressive episode include depressed mood; markedly diminished interest or pleasure in all, or almost all, activities most of the day; weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day; insomnia or hypersomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt nearly every day; diminished ability to think or concentrate, or indecisiveness, nearly every day; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Further, the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, American Psychiatric Association, 1994)

Current treatment options for unipolar depression include monotherapy or combination therapy with various classes of drugs including mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitor, "natural products" (such as Kava-Kava, St. John's Wort), dietary supplement (such as s-adenosylmethionine) and others. More specifically, drugs used in the treatment of depression include, but are not limited to imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, maprotiline, amoxapine, trazodone, bupropion, chlomipramine, fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, nefazadone, venlafaxine, reboxetine, mirtazapine, phenelzine, tranlycypromine, and / or moclobemide (eg, J.M. KENT, *Lancet* 2000, 355, 911-918;

J.W. WILLIAMS JR, C.D. MULROW, E. CHIQUETTE, P.H. NOEL, C. AGUILAR, and J. CORNELL, *Ann. Intern. Med.* **2000**, *132*, 743-756; P.J. AMBROSINI, *Psychiatr. Serv.* **2000**, *51*, 627-633). Several of these agents including, but not limited to, serotonin reuptake inhibitors are also used when depression and anxiety co-exist, such as in anxious depression (R.B. LYDIARD and O. BRAWMAN-MINTZER, *J. Clin. Psychiatry* **1998**, *59*, Suppl. 18, 10-17; F. ROUILLON, *Eur. Neuropsychopharmacol.* **1999**, *9* Suppl. 3, S87-S92).

In the clinic, 40-50% of depressed patients who are initially prescribed antidepressant therapy do not experience a timely remission of depression symptoms. This group typifies treatment-refractory depression, that is, a failure to demonstrate an "adequate" response to an "adequate" treatment trial (that is, sufficient intensity of treatment for sufficient duration) (R.M. BERMAN, M. NARASIMHAN, and D.S. CHARNEY, *Depress. Anxiety* **1997**, *5*, 154-164). Moreover, about 20-30% of depressed patients remain partially or totally resistant to pharmacological treatment including combination treatments (J. ANANTH, *Psychother. Psychosom.* **1998**, *67*, 61-70; R.J. CADIEUX, *Am. Fam. Physician* **1998**, *58*, 2059-2062). Increasingly, treatment of resistant depression includes augmentation strategies including treatment with pharmacological agents such as, lithium, carbamazepine, and triiodothyronine, and the like (M. HATZINGER and E. HOLSBOER-TRACHSLER, *Wien. Med. Wochenschr.* **1999**, *149*, 511-514; C.B. NEMEROFF, *Depress. Anxiety* **1996-1997**, *4*, 169-181; T.A. KETTER, R.M. POST, P.I. PAREKH and K. WORTHINGTON, *J. Clin. Psychiatry* **1995**, *56*, 471-475; R.T. JOFFE, W. SINGER, A.J. LEVITT, C. MACDONALD, *Arch. Gen. Psychiatry* **1993**, *50*, 397-393).

Dysthymia is defined as a mood disorder characterized by chronic depressed mood for a period of at least 2 years. Dysthymia can have a persistent or intermittent course and the depressed mood occurs for most of the day, for more days than not, and for at least 2 years. (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, American Psychiatric Association, **1994**).

Bipolar disorder, on the other hand, is characterized by unpredictable swings in mood between mania and depression (bipolar I disorder) or between hypomania and depression (bipolar II disorder) (*Diagnostic and Statistical Manual of Mental*

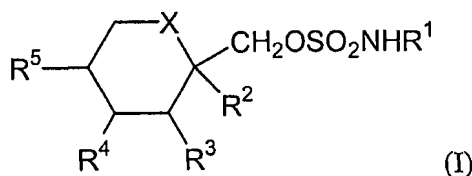
Disorders, 4th Edition, American Psychiatric Association, 1994). Antidepressant use in bipolar disorder is generally, intentionally restricted to avoid the risk of mania and the risk of rapid cycling induced by antidepressants in bipolar disorder (H.J. MOLLER and H. GRUNZE, *Eur. Arch. Psychiatry Clin. Neurosci.* **2000**, *250*, 57-68; J.R.

- 5 CALABRESE, D.J. RAPPORT, S.E. KIMMEL, and M.D. SHELTON, *Eur. Neuropsychopharmacol.* **1999**, *9*, S109-S112). Moreover, none of the mood stabilizers used in bipolar disorder have proven antidepressive efficacy (H.J. MOLLER and H. GRUNZE, *Eur. Arch. Psychiatry Clin. Neurosci.* **2000**, *250*, 57-68).

10

DISCLOSURE OF THE INVENTION

Accordingly, it has been found that compounds of the following formula (I):



- wherein X is O or CH₂, and R¹, R², R³, R⁴ and R⁵ are as defined hereinafter are useful in treating depression, specifically unipolar depression, treatment-refractory depression, resistant depression, anxious depression and dysthymia.
- 15

In an embodiment of the present invention, the depression is selected from the group consisting of unipolar depression, treatment refractory depression, resistant depression and anxious depression.

- 20 In an embodiment of the present invention is a method for the treatment of depression comprising administering to a subject in need thereof a combination of one or more compounds of formula I with one or more compounds selected from the group consisting of mono-amine oxidase inhibitors such as phenelzine, tranylcypromine, moclobemide, and the like; tricyclics such as imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlomipramine, amoxapine, and the like; tetracyclics such as maprotiline, and the like; non-cyclics such as nomifensine, and the like; triazolopyridines such as trazodone, and the like; serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, and the like; serotonin receptor antagonists such as nefazadone, and the like; serotonin
- 25
- 30 noradrenergic reuptake inhibitors such as venlafaxine, milnacipran and the like;

noradrenergic and specific serotonergic agents such as mirtazapine, and the like;
noradrenaline reuptake inhibitors such as reboxetine, and the like; atypical
antidepressants such as bupropion, and the like; natural products such as Kava-Kava,
St. John's Wort, and the like; dietary supplements such as s-adenosylmethionine., and
5 the like; and neuropeptides such as thyrotropin-releasing hormone and the like, and the
like; compounds targeting neuropeptide receptors such as neurokinin receptor
antagonists and the like; and hormones such as triiodothyronine, and the like.

In an embodiment of the present invention is a method for the treatment of
10 depression comprising administering to a subject in need thereof a combination of one
or more compounds of formula I with one or more compounds selected from the group
consisting of mono-amine oxidase inhibitors; tricyclics; tetracyclics; non-cyclics;
triazolopyridines; serotonin reuptake inhibitors; serotonin receptor antagonists;
serotonin noradrenergic reuptake inhibitors; serotonin noradrenergic reuptake
15 inhibitors; noradrenergic and specific serotonergic agents; noradrenaline reuptake
inhibitors; atypical antidepressants; natural products; dietary supplements;
neuropeptides; compounds targeting neuropeptide receptors; and hormones.

Preferably, one or more compounds of formula I are administered in
combination with one or more compounds selected from the group consisting of mono-
20 amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin
noradrenergic reuptake inhibitors; noradrenergic and specific serotonergic agents and
atypical antidepressants.

More preferably, one or more compounds of formula I are administered in
combination with one or more compounds selected from the group consisting of mono-
25 amino oxidase inhibitors, tricyclics and serotonin reuptake inhibitors.

Most preferably, one or more compounds of formula I are administered in
combination with one or more compounds selected from the group consisting of
serotonin reuptake inhibitors.

30 In an embodiment of the present invention is a method for the treatment of
depression comprising administering to a subject in need thereof a combination of one
or more compounds of formula I with one or more compounds selected from the group
consisting of phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline,

desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlormipramine, amoxapine, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, venlafaxine, milnacipran, mirtazapine, bupropion, thyrotropin-releasing hormone and triiodothyronine.

5 Preferably, one or more compounds of formula I are administered in combination with one or more compounds selected from the group consisting of phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlormipramine, amoxapine, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, venlafaxine, milnacipran, 10 mirtazapine and bupropion.

 More preferably, one or more compounds of formula I are administered in combination with one or more compounds selected from the group consisting of phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlormipramine, amoxapine, 15 fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine.

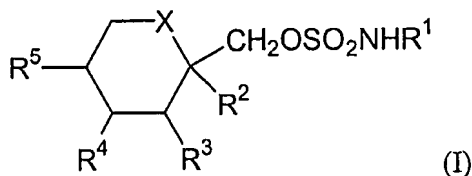
 Most preferably, one or more compounds of formula I are administered in combination with one or more compounds selected from the group consisting of fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine.

20 In an embodiment of the present invention, is a method for the treatment of depression comprising administering to a subject in need thereof a combination of one or more compounds of formula I with one or more compounds selected from the group consisting of neuropeptides such as thyrotropin-releasing hormone and the like; compounds targeting neuropeptide receptors such as neurokinin receptors antagonists 25 and the like; and hormones such as triiodothyronine and the like.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

 As used herein, the term "depression" shall be defined as unipolar depression, treatment-refractory depression, resistant depression, anxious depression and 30 dysthymia.

 The sulfamates of the invention are of the following formula (I):

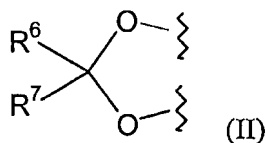


wherein

X is CH₂ or oxygen;

R¹ is hydrogen or alkyl; and

- 5 R², R³, R⁴ and R⁵ are independently hydrogen or lower alkyl and, when X is CH₂, R⁴ and R⁵ may be alkene groups joined to form a benzene ring and, when X is oxygen, R² and R³ and/or R⁴ and R⁵ together may be a methylenedioxy group of the following formula (II):



- 10 wherein

R⁶ and R⁷ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

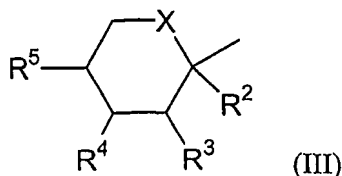
- 15 R¹ in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R², R³, R⁴, R⁵, R⁶ and R⁷ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH₂, R⁴ and R⁵ may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R⁴ and R⁵ are defined by the alkatrienyl group =C-CH=CH-CH=.

20

- A particular group of compounds of formula (I) is that wherein X is oxygen and both R² and R³ and R⁴ and R⁵ together are methylenedioxy groups of the formula (II), wherein R⁶ and R⁷ are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R⁶ and R⁷ are both alkyl such as methyl. A second group of compounds is that wherein X is CH₂ and R⁴ and R⁵ are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R² and R³ are hydrogen.
- 25

The compounds of formula (I) may be synthesized by the following methods:

- (a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR^1$ in the presence of a base such as potassium *t*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF, or dimethylformamide wherein R is a moiety of the following formula (III):



- (b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl .

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R^1NH_2 at a temperature of about 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in *Tetrahedron Lett.*, **1978**, 3365.

- (c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M. Hedayatullah in *Tetrahedron Lett.* **1975**, 2455. The azidosulfate is then reduced to a compound of formula (I) wherein R^1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R^2 and R^3 and R^4 and R^5 are identical and are of the formula (II) may be

obtained by the method of R. F. Brady in *Carbohydr. Res.* **1970**, *14*, 35 or by reaction of the trimethylsilyl enol ether of a R⁶COR⁷ ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al. in *J. Org. Chem.* **1973**, *38*, 3935.

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH₂OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed US Patents: No.4,513,006, No.5,242,942, and No.5,384,327, which are incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R², R³, R⁴ and R⁵ on the 6-membered ring. Preferably, the oxygen of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The ability of the compounds of formula I to treat depression is based on the results of clinical case studies in which topiramate was added to existing pharmacotherapy in two patients with diagnosed depression.

EXAMPLE 1

In the first case, the patient was a female who had suffered from depression for 25 years. In addition, the patient exhibited anxiety, sensitivity to her environment, and presented with a history of migraine headaches, obesity and two suicide attempts.

5 Previous pharmacological treatment history included unsuccessful treatment of patient's depression with the combination of clomipramine + lithium + carbamazepine and only partial response with the combinations of imipramine + fluoxetine + carbamazepine and venlafaxine + mirtazapine.

Topiramate was prescribed for the patient as add-on therapy to existing treatment of venlafaxine at 225 mg/day and mirtazapine at 30 mg/day. Topiramate
10 treatment was initiated at 25 mg/day, with increased dosage to 150 mg/day. After two months, with topiramate dosage at 150 mg/day, the patient was reevaluated as "very mild depressive". After six months, mirtazapine was withdrawn and topiramate daily dosage increased to 200 mg/day. At this point, the patient was evaluated as "very much improved". Topiramate dosage was further increased to 300 mg/day and after
15 eight months patient's depression was "very much improved".

Following one year, topiramate and venlafaxine were withdrawn because of a surgical procedure. The patient experienced relapse in depression, binge eating symptoms and body weight gain. The patient was subsequently restarted on topiramate at 300 mg/day. Following six months of treatment, the patient reported "feeling very
20 well", had reduced anxiety and depression, with increased initiative and confidence.

EXAMPLE 2

In the second case, the patient was a female who had suffered from depression, binge eating and obesity for 11 years. In addition, the patient exhibited anxiety,
25 aggression and sensitivity to her environment. She had no history of mania or hypomania and no relatives with bipolar disorder.

Previous pharmacological treatment history included unsuccessful treatment of patient's depression with amitriptyline, tranlycypromine and the combination therapies of fluoxetine + nortriptyline + triiodothyronine and paroxetine + carbamazepine +
30 amphetamine.

The patient's depression appeared controlled with a combination of 300 mg/day venlafaxine, 800 mg/day carbamazepine, 40 mg/day methylphenidate and 2 mg/day

risperidone. However, the patient experienced mild relapses of depression over a period of about two years.

Initially the patient was started on topiramate add-on therapy at 25 mg/day, with increased dosage to 150 mg/day over the course of one month, in response to the patient's clinical behavior (the patient experienced suicidal ideation). One month later, the topiramate therapy was further increased to 300 mg/day, with the patient also taking 20 mg/day methylphenidate and 150 mg/day venlafaxine. At this time the patient was rated "much improved", with resolved suicidal ideation. After three months of treatment, the patient reported that she had "never felt so well". She had clear thoughts, good concentration, better performance at work, and felt less tired. Her feelings of hostility and hypersensitivity to the environment had also resolved. At eight months of therapy, she continued to be normothymic and to feel very well. Compared with her state of well-being on commencing of treatment, she felt happier, had more pleasure and interests, was outgoing, energetic and creative, had better memory and concentration, normal libido, less irritability, and improved social and work performance. By this time the patient was only taking venlafaxine at 150 mg/day and topiramate at 300 mg/day.

Thus, for treating depression, a compound of formula I may be employed by administering repeated oral doses in the range of about 10 to 650 mg daily, more preferably in the range of about 16 to 325 mg once or twice daily. Further, for treating depression, the compound of formula I may be used as monotherapy or as a component in combination therapy.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound or compounds used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and concomitant diseases, will result in the need to adjust dosages.

As used herein, the term "subject" shall refer to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

5 As used herein, the term "therapeutically effective amount" means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

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As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amount, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amount.

15

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula I are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for
20 administration, e.g., i.v. sterile injectable formulations will be prepared using appropriate solubilizing agents. A unit dose would contain about 15 to 200 mg of the active ingredient. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain some or all of the following inactive ingredients: lactose hydrous, pregelatinized starch,
25 microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

Wherein the present invention is directed to pharmaceutical administration of
30 one or more compounds of formula I, the compound(s) of formula I may be administered by any suitable method, as would be apparent to one skilled in the art. More particularly, the compound(s) of formula I may be administered by any parenteral method including, but not limited to oral pulmonary, intraperitoneal (ip), intravenous

(iv), intramuscular (im), subcutaneous (sc), transdermal, buccal, nasal, sublingual, ocular, rectal and vaginal. The compounds(s) of formula I, including topiramate, may also be administered directly to the nervous system, including but not limited to, via intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and/or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and/or catheters with or without pump devices. It will be readily apparent to those skilled in the art that any dose or frequency of administration that provides the therapeutic effect described herein is suitable for use in the present invention.

10

In certain embodiments of the present invention, the compound of formula I may be administered in combination with one or more compounds as previously described, preferably in combination with one to three compounds, more preferably in combination with one to two compounds.

15

Wherein the present invention is directed to the administration of a combination, the compounds may be co-administered simultaneously, sequentially, separately or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently. Further, the compounds may be administered via the same or different routes of administration, and at the same or different times during the course of the therapy, concurrently in divided or single combination forms. The instant invention is therefore understood as embracing all regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

25

Wherein the present invention is directed to therapy with a combination of agents, "therapeutically effective amount" shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of combination therapy comprising a compound of formula I and a serotonin reuptake inhibitor would be the amount of the compound of formula I and the amount of the serotonin reuptake

30

inhibitor that when taken together or sequentially have a combined effect that is therapeutically effective, more preferably where the combined effect is synergistic. Further, it will be recognized by one skilled in the art that in the case of combination therapy with a therapeutically effect amount, the amount of each component of the combination individually may or may not be therapeutically effective.

Therapeutically effective dosage levels and dosage regimens for mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitor, natural products, dietary supplements, neuropeptides, compounds targeting neuropeptide receptors, hormones and other pharmaceutical agents disclosed herein, may be readily determined by one of ordinary skill in the art. For example, therapeutic dosage amounts and regimens for pharmaceutical agents approved for sale are publicly available, for example as listed on packaging labels, in standard dosage guidelines, in standard dosage references such as the Physician's Desk Reference (Medical Economics Company or online at <http://www.pdrel.com>) or other sources.

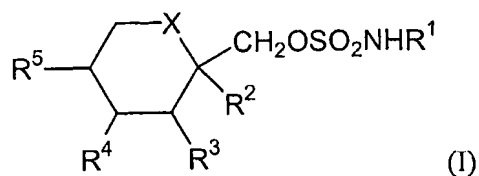
To prepare a pharmaceutical composition of the present invention wherein the compound of formula I is administered in combination with one or more compounds as previously described, the dosages of the individual compounds are selected in such a manner as to provide effective levels of each of the compounds in the body at the same time and may vary depending on the particular compound administered and general and specific responses to the compound. Further, the ratio of the compounds may be varied as to optimize therapeutic synergy. Wherein the compounds are administered in a single dosage form, the pharmaceutical composition may be prepared according to conventional pharmaceutical compounding techniques and may include intimately admixing the active compounds with one or more pharmaceutical carriers, excipients and / or additives.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variation, adaptations

and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating depression in a subject afflicted with such condition comprising administering to the subject a therapeutically effective amount of a
 5 compound of the formula I:

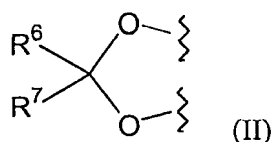


wherein

X is CH₂ or oxygen;

R¹ is hydrogen or alkyl; and

- 10 R², R³, R⁴ and R⁵ are independently hydrogen or lower alkyl and, when X is CH₂, R⁴ and R⁵ may be alkene groups joined to form a benzene ring and, when X is oxygen, R² and R³ and/or R⁴ and R⁵ together may be a methylenedioxy group of the following formula (II):

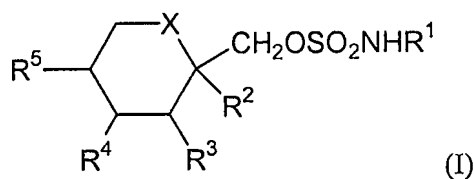


- 15 wherein

R⁶ and R⁷ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.
 20
3. The method of claim 1, wherein the therapeutically effective amount is from about 10 to 650 mg daily.
4. The method of claim 1, wherein the amount is from about 16 to 325 mg once or
 25 twice daily.
5. The method of Claim 1, wherein the depression is unipolar depression.

6. The method of Claim 1, wherein the depression is treatment-refractory depression.
7. The method of Claim 1, wherein the depression is resistant depression.
- 5 8. The method of Claim 1, wherein the depression is anxious depression.
9. The method of Claim 1, wherein the depression is dysthymia.
- 10 10. A method for treating depression in a subject afflicted with such condition comprising administering to the subject a therapeutically effective amount of a compound of the formula I



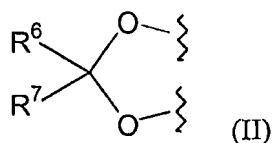
wherein

- 15 X is CH₂ or oxygen;

R¹ is hydrogen or alkyl; and

R², R³, R⁴ and R⁵ are independently hydrogen or lower alkyl and, when X is CH₂, R⁴ and R⁵ may be alkene groups joined to form a benzene ring and, when X is oxygen, R² and R³ and/or R⁴ and R⁵ together may be a methylenedioxy group of the

- 20 following formula (II):



wherein

R⁶ and R⁷ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

- 25

in combination with one or more compounds selected from the group consisting of mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents,

noradrenaline reuptake inhibitor, natural products, dietary supplements, neuropeptides, compounds targeting neuropeptide receptors and hormones.

11. The method of Claim 10 wherein the compound of formula I is administered in
5 combination with one or more compounds selected from the group consisting of
imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline,
trimipramine, maprotiline, amoxapine, trazodone, bupropion, chlomipramine,
fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, nefazadone, venlafaxine,
milnacipran, reboxetine, mirtazapine, phenelzine, tranylcypromine, moclobemide,
10 Kava-Kava, St. John's Wart, s-adenosylmethionine, thyrotropin releasing hormone,
neurokinin receptor antagonists and triiodothyronine.

12. The method of Claim 10, wherein the compound of formula I is topiramate.

15 13. The method of Claim 10, wherein the therapeutically effective amount is from
about 10 to 650 mg daily.

14. The method of Claim 10, wherein the amount is from about 16 to 325 mg once
or twice daily.

20 15. The method of Claim 10, wherein the compound of formula I is topiramate and
is administered in combination with one or more compounds selected from the group
consisting of mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors,
serotonin noradrenergic reuptake inhibitors; noradrenergic and specific serotonergic
25 agents and atypical antidepressants.

16. The method of Claim 15 wherein the compound of formula I is topiramate and
is administered in combination with one or more compounds selected from the group
consisting of phenelzine, tranylcypromine, moclobemide, imipramine, amitriptyline,
30 desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlomipramine,
amoxapine, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, venlafaxine,
milnacipran, mirtazapine and bupropion.

17. The method of Claim 10, wherein the compound of formula I is topiramate and is administered in combination with one or more compounds selected from the group consisting of neuropeptides, compounds targeting neuropeptide receptors and hormones.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/23786

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/255 A61K31/35 A61K31/7048 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, MEDLINE, BIOSIS, SCISEARCH, EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DURSUN S M ET AL: "Accelerated weight loss after treating refractory depression with fluoxetine plus topiramate: possible mechanisms of action?" CANADIAN JOURNAL OF PSYCHIATRY. REVUE CANADIENNE DE PSYCHIATRIE, (2001 APR) 46 (3) 287-8., XP001029971 the whole document --- -/--	1-17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/23786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 62522 A (TOLLEFSON GARY DENNIS ;LILLY CO ELI (US)) 9 December 1999 (1999-12-09) cited in the application abstract page 2, line 9 - line 17 page 6, line 23 - line 25 page 7, line 12 - line 17 page 18, line 8 - line 9; claims 1,12-14</p>	1-17
X	<p>--- DATABASE ADISALERTS 'Online! PRADO LIMA P A S ET AL: "Topiramate in treatment-refractory depression" retrieved from STN Database accession no. 1999:61852 XP002179442 abstract & 11TH WORLD CONGRESS OF PSYCHIATRY (AUG 6, 1999), VOL. 2, PP. 126,</p>	1-17
X	<p>--- GARONNA F ET AL: "Topiramate in the treatment of over-weight/obese binge eaters ADIS TITLE: Topiramate: therapeutic use.;Obesity; In patient with binge eating disorders" INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY INT J NEUROPSYCHOPHARMACOL 3 (SUPPL. 1): 299, JUL 2000. (JUL 1, 2000), XP001030426 Bassano d/G, Vicenza, Italy the whole document</p>	1-17
X	<p>--- DATABASE ADISALERTS 'Online! MCELROY S L ET AL: "A pilot trial of adjunctive topiramate in the treatment of bipolar disorder ADIS TITLE: Topiramate: therapeutic use.;Bipolar disorder; A pilot trial of adjunctive treatment" retrieved from STN Database accession no. 1998:39968 XP002179443 abstract & XXIST CINP CONGRESS (JUL 12, 1998), PP. 281 (POSTER), University of Cincinnati College of Medicine, Cincinnati, Ohio, USA --- -/--</p>	1-17

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/23786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE DRUGNL 'Online! "Topiramate" retrieved from STN Database accession no. 1998:2562 XP002179444 abstract & R&D FOCUS DRUG NEWS, 27 July 1998 (1998-07-27), ---</p>	1-17
X	<p>WO 98 00123 A (ORTHO PHARMA CORP) 8 January 1998 (1998-01-08) cited in the application the whole document ---</p>	1-17
Y	<p>SANACORA G. ET AL: "Impairment of GABAergic transmission in depression: New insights from neuroimaging studies." CRITICAL REVIEWS IN NEUROBIOLOGY, (2000) 14/1 (23-45)., XP001029967 the whole document ---</p>	1-17
Y	<p>KUZIECKY R ET AL: "TOPIRAMATE INCREASE CEREBRAL GABA IN HEALTHY HUMANS" NEUROLOGY, LIPPINCOTT WILLIAMS & WILKINS, PHILADELPHIA, US, no. 51, August 1998 (1998-08), pages 627-629, XP000923467 ISSN: 0028-3878 the whole document ---</p>	1-17
Y	<p>KYOWA HAKKO: "TOPIRAMATE" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 21, no. 4, 1996, pages 463-465, XP002043895 ISSN: 0377-8282 the whole document ---</p>	1-17
A	<p>US 4 513 006 A (MARYANOFF BRUCE E ET AL) 23 April 1985 (1985-04-23) cited in the application the whole document ---</p>	1-17
A	<p>LANGTRY H.D. ET AL: "Topiramate. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy." DRUGS, (1997) 54/5 (752-773)., XP002179441 the whole document -----</p>	1-17

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/23786

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9962522	A	09-12-1999	AU 4008899 A BR 9911068 A CN 1302207 T EP 0966967 A2 NO 20005884 A WO 9962522 A1	20-12-1999 06-02-2001 04-07-2001 29-12-1999 24-01-2001 09-12-1999
WO 9800123	A	08-01-1998	AU 3409697 A CA 2258895 A1 CZ 9804277 A3 EP 0932398 A1 NO 986051 A WO 9800123 A1 US 5753693 A ZA 9705773 A	21-01-1998 08-01-1998 11-08-1999 04-08-1999 23-02-1999 08-01-1998 19-05-1998 28-12-1998
US 4513006	A	23-04-1985	AT 36149 T AU 564842 B2 AU 3350484 A CA 1241951 A1 DE 3473143 D1 DK 198191 A ,B, DK 198291 A DK 457784 A ,B, EP 0138441 A2 ES 536225 D0 ES 8602634 A1 FI 843765 A ,B, HU 36784 A2 IE 57684 B1 JP 1804249 C JP 5005824 B JP 60109558 A JP 5331132 A KR 9201775 B1 MX 9202630 A1 NO 843836 A ,B, NZ 209494 A US 4582916 A ZA 8407550 A	15-08-1988 27-08-1987 04-04-1985 13-09-1988 08-09-1988 09-12-1991 09-12-1991 27-03-1985 24-04-1985 16-11-1985 16-03-1986 27-03-1985 28-10-1985 24-02-1993 26-11-1993 25-01-1993 15-06-1985 14-12-1993 02-03-1992 30-06-1992 27-03-1985 06-03-1987 15-04-1986 28-05-1986

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WO 03/097046 A1

(54) Title: METHOD FOR TREATING OBESITY

(57) Abstract: The present invention relates, in general, to obesity, and, in particular, to a method of treating obesity and minimizing metabolic risk factors associated therewith using, for example, zonisamide or other weight-loss promoting anticonvulsant either alone or in combination with bupropion or other compound that enhances the activity of norepinephrine and/or dopamine via uptake inhibition or other mechanism.

METHOD FOR TREATING OBESITY

This application claims priority from Prov. Appln. No. 60/380,874, filed May 17, 2002, the content of which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates, in general, to obesity, and, in particular, to a method of treating obesity and minimizing metabolic risk factors associated therewith using, for example, zonisamide or other weight-loss promoting anticonvulsant either alone or in combination with bupropion or other compound that enhances the activity of norepinephrine and/or dopamine via uptake inhibition or other mechanism.

BACKGROUND

The prevalence of obesity has risen significantly in the past decade in the United States and many other developed countries, (Fiegal et al, Int. J. Obesity 22:39-47 (1998), Mokdad et al, JAMA 282:1519-1522 (1999)). Because obesity is associated with a significantly elevated risk for type 2 diabetes, coronary heart disease, hypertension, and numerous other major illnesses, and overall mortality from all causes (Must et al, JAMA 282:1523-1529 (1999), Calle et al, N. Engl. J. Med. 341:1097-1105 (1999)), weight

reduction is critical for the obese patient (Blackburn, Am. J. Clin. Nutr. 69:347-349 (1999), Galuska et al, JAMA 282:1576 (1999)). There is good evidence that pharmacotherapy can enhance weight loss when combined with interventions aimed at changing life style (National Heart, Lung and Blood Institute, Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report, NIH Publication No. 98-4083, Sept. 1998). Yet, the available pharmacological therapies to facilitate weight loss fail to provide adequate benefit to many obese patients because of side effects, contraindications or lack of positive response (National Heart, Lung and Blood Institute, Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report, NIH Publication No. 98-4083, Sept. 1998). Hence, there is impetus for developing new and alternative treatments for management of obesity.

Zonisamide (ZONEGRAN®) is a marketed antiepileptic drug (AED). In short-term clinical trials of zonisamide in epileptic patients taking other concomitant AEDs, a small degree of weight loss was observed as an adverse effect in a small percent of patients (Oommen and Matthews, Clin. Neuropharmacol. 22:192-200 (1999)). The anticonvulsant activity of zonisamide is believed to be related to its sodium and calcium channel (T-type)

channel blocking activity (Oommen and Matthews, Clin. Neuropharmacol. 22:192-200 (1999)). This drug is also known to exert dopaminergic (Okada et al, Epilepsy Res. 22:193-205 (1995)) as well as dose-dependent biphasic serotonergic activity (Okada et al, Epilepsy Res. 34:187-197 (1999)).

Topiramate (TOPAMAX®) is an AED that has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy in treating simple and complex partial seizures and secondarily generalized seizures (Faught et al, Epilepsia 36(S4):33 (1995); Sachdeo et al, Epilepsia 36(S4):33 (1995)). It is currently marketed as adjunctive therapy for partial onset seizures or primary generalized tonic-clonic seizures.

Bupropion, marketed as an antidepressant, has a pharmacological action dissimilar to that of zonisamide or topiramate. Bupropion has been shown to cause significant weight loss in patients presenting with primary obesity (Gadde et al, Obes. Res. 9(9):544 (2001)).

The present invention results, at least in part, from studies demonstrating that zonisamide is more effective than placebo for weight loss in obese subjects. The use of zonisamide (or other weight-loss promoting anticonvulsant) and bupropion (or other compound that enhances monoamine (e.g., serotonin, norepinephrine and/or dopamine) turnover in the brain

via uptake inhibition or other mechanism) provides an effective treatment for obesity with few side effects.

SUMMARY OF THE INVENTION

The present invention relates generally to obesity. More specifically, the invention relates to a method of treating obesity and minimizing metabolic risk factors associated therewith using, for example, zonisamide or other weight loss-promoting anti-convulsant either alone or in combination with bupropion or other compound that enhances the activity of norepinephrine and/or dopamine via uptake inhibition or other mechanism.

Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Disposition of study subjects.

Figure 2. Pattern of weight change from baseline to Week 16 in obese subjects who received zonisamide (n=30) or placebo (n=30). Results plotted as means (SE). Data are from the last observation-carried-forward (LOCF) analysis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating obesity in an animal. The invention further relates to a method of minimizing metabolic risk factors associated with obesity, such as hypertension, diabetes and dyslipidaemia. In one embodiment, the methods comprise administering to an animal in need of such treatment an effective amount of zonisamide or other weight-loss promoting anticonvulsant. In an alternative embodiment, the methods comprise administering a combination of zonisamide or topiramate, or other weight-loss promoting anticonvulsant (including agents that block kainate/AMPA (D,L- α -amino-3-hydroxy-5-methyl-isoxazole propionic acid) subtype glutamate receptors), and bupropion, or other compound that enhances the activity of norepinephrine and/or dopamine via uptake inhibition or other mechanism, in effective amounts.

Preferred active agents for use in the present invention include zonisamide or topiramate (and pharmaceutically acceptable salts thereof), however, other methane-sulfonamide derivatives, such as those described in USP 4,172,896, or other sulfamates (including sulfamate-substituted monosaccharides), such as those described in USP 4,513,006, can also be used. While the use of bupropion is also preferred, compounds disclosed in USP 3,819,706 and 3,885,046 can

be used, as can other compounds that enhance the activity of norepinephrine and/or dopamine via uptake inhibition or other mechanism (e.g., Atomoxetine or Reboxetine).

As used herein, the term "obesity" includes both excess body weight and excess adipose tissue mass in an animal. An obese individual is one (e.g., 21-50 years old) having a body mass index of ≥ 30 kg/m². While the animal is typically a human, the invention encompasses the treatment of non-human mammals.

The amount of active agent(s) (e.g., zonisamide alone or in combination with, for example, bupropion) administered can vary with the patient, the route of administration and the result sought. Optimum dosing regimens for particular patients can be readily determined by one skilled in the art.

When zonisamide is used alone, the dose can be from about 25mg to about 800mg per day, generally given once per day or divided (e.g., equally) into multiple doses. Preferably, the dose is from about 100mg to about 600mg per day, more preferably, the dose is from about 200mg to about 400mg per day. However, it may be necessary to use dosages outside these ranges.

When the combination therapy is used, the daily dose of, for example, zonisamide can be from about 25mg to about 800mg, preferably from about 100mg to about 600mg, more preferably from about 200mg to about

400mg. When topiramate is used in combination therapy, the daily dose of topiramate can be from about 25mg to about 1600mg, preferably from about 50mg to about 600mg, more preferably from about 100mg to about 400mg. The daily dose of bupropion used can be from about 25mg to about 600mg, preferably from about 50mg or about 150mg to about 450mg. The doses can be given once per day or divided (e.g., equally) into multiple doses. It may be necessary to use dosages outside these ranges. When the combination therapy is used, the ratio of zonisamide (or topiramate) to bupropion can range, for example, from about 2:1 to about 1:2.

When the combination therapy is used, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

In accordance with the present invention, the active agent(s) (e.g., zonisamide alone or in combination with bupropion) can be administered in any convenient manner, such as orally, sublingually, rectally, parentally (including subcutaneously, intrathecal, intramuscularly and intravenously), or transdermally. The most preferred route of administration is the oral route.

The active agents of the invention can be administered in the form of a pharmaceutical

composition or compositions that contain one or both in an admixture with a pharmaceutical carrier. The pharmaceutical composition can be in dosage unit form such as tablet, capsule, sprinkle capsule, granule, powder, syrup, suppository, injection or the like. Sustained released formulations can also be used. The composition can also be present in a transdermal delivery system, e.g., a skin patch.

Details of appropriate routes of administration and compositions suitable for same can be found in, for example, USPs 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

In accordance with the invention, the combination of, for example, zonisamide or topiramate and bupropion (including sustained release preparations) is an effective treatment for obesity and provides an effective means of minimizing metabolic risks associated with obesity. The combination can be more effective than, for example, zonisamide or topiramate treatment alone and with fewer side effects. Neuropharmacologically, all three major nerve transmitters that regulate appetite and weight, i.e., serotonin, norepinephrine and dopamine, are targeted with the combination of, for example, bupropion and zonisamide or topiramate. Side effects of, for example, zonisamide or topiramate (such as somnolence, psychomotor slowing, cognitive impairment, fatigue and

depression) can be offset by insomnia, activation, psychomotor agitation and antidepressant effects of, for example, bupropion. On the other hand, zonisamide or topiramate, for example, can reduce the seizure risk associated with, for example, bupropion. Lower doses of both types of medication can be used in the combination treatment, thereby further reducing the overall side effect burden.

Certain aspects of the invention are described in greater detail in the non-limiting Examples that follow and in Gadde et al, JAMA 289:1820 (2003). (See also USPs 6,323,236, 6,071,537, 6,548,551, 6,506,799 and 6,191,117.)

EXAMPLE 1

Experimental Details

Subjects

Sixty-eight subjects were screened for participation and 60 subjects were randomized.

Inclusion criteria were: male or female, aged 21-50 years, with body mass index (BMI) of ≥ 30 kg/m².

Exclusion criteria were: obesity of a known endocrine origin, such as hypothyroidism and Cushing's syndrome; serious/unstable medical or psychiatric illness; current major psychiatric disorder; current drug or alcohol abuse; history of or current kidney disease or renal calculi; significant liver disease; uncontrolled hypertension; current diabetes mellitus

(DM), type 1 or 2 DM receiving pharmacotherapy; untreated or uncontrolled thyroid disease; weight loss or gain greater than four kilograms in past three months; history of obesity surgery; current or recent use of any weight loss medications, herbs, or supplements; current or recent use of drugs, herbs, or dietary supplements known to significantly affect body weight; concomitant medications that significantly affect P450 3A4 hepatic microsomal enzymes; hypersensitivity to sulfonamides; women of child-bearing age not adhering to an acceptable form of contraception; pregnant or breast-feeding women; and, subjects judged to be unable to follow instructions and study procedures.

Study design

The study had two phases. The first was the acute phase - a 16-week, randomized, double blind, parallel-group comparison of zonisamide (ZON) and placebo (PBO). This was followed by an optional 16-week extension phase. At the end of the acute phase, subjects wishing to continue further received the same treatment for an additional 16 weeks in a single-blinded fashion.

Randomization, medication dosing and dispensing

The subjects were randomized in a 1:1 ratio to receive zonisamide or placebo capsules. Study medication was dispensed under blinded conditions

through computer-based randomization. The randomization was generated using a random number table with a block size of ten. There was no stratification by gender or other demographics. The study investigators were blind to the "blocking" method used by the pharmacy. The treatment assignment codes were not available to the investigators until all subjects completed the acute phase, the data were entered, and the database for this phase was locked, meaning that no further changes could be made to the data.

The study medication was dispensed in the form of capsules. Each capsule contained either 100 milligrams zonisamide or placebo. The capsules were made to look identical. The dose escalation was as follows: one capsule (zonisamide 100 mg or placebo) every evening for the first 2 weeks; two capsules (zonisamide 200 mg or placebo) every evening during Weeks 3 and 4; three capsules (zonisamide 300 mg or placebo) every evening during Weeks 5 and 6; and, four capsules (zonisamide 400 mg or placebo) every evening from Week 7 onward. At Week 12, the dose could be increased further to six capsules (zonisamide 600 mg or placebo) every evening for subjects who had not lost at least 5% of their initial body weight. If a subject preferred not to take all six capsules at one time, taking a half of the daily dose in the morning was an option. Based on tolerability, dose escalation

could be withheld, or the dose might also be decreased. Medication compliance was overseen by recording the number of tablets returned and comparing this number to the number of capsules dispensed at each visit.

Diet and lifestyle counseling

Subjects in both treatment groups were instructed to follow an individual diet that was 500 Kcal/day less than what they needed to maintain their weight. The prescribed diet, based on eating a variety of foods from the Food Guide Pyramid, emphasized decreasing portions, eating more fruits and vegetables, and drinking 8 cups of water each day. Increased physical activity was also encouraged for subjects in both groups. Subjects were asked to record their dietary intake including portion sizes in food diaries, which were provided to them. A registered dietician reviewed food diaries and provided counseling to all subjects. Subjects were encouraged to make healthy changes in their diets and physical activity that could be maintained after the completion of the study.

Visits and measurements

Subjects were seen at weeks 0, 2, 4, 8, 12, and 16 in the acute phase, and every four weeks in the extension phase. During each visit, the following assessments were performed: blood pressure, heart

rate, weight, dietary compliance, medication accountability and tolerability, and adverse effects. Body weight was measured on a calibrated electronic scale to the nearest 0.1 kilogram. A registered dietitian reviewed food diaries and assessed dietary compliance. Adverse effects were gathered via spontaneous reporting by subjects as well as open-ended inquiries by the clinicians. Reportable adverse effects were new symptoms or illnesses that emerged during treatment or those that had an increase in severity compared with baseline.

In addition to the above, the subjects completed the Impact of Weight on Quality of Life (IWQOL) (Kolotin et al, Obesity Res. 3:49-56 (1995)) at baseline, Week 8, and Week 16. The IWQOL is a self-report measure with 74 items that assess the perceived effect of weight on quality of life in the following domains (subscales) - health, social/interpersonal life, work, mobility, self-esteem, sexual life, activities of daily living, and eating (comfort with food). Improvement with treatment is reflected by decreasing scores on all the subscales with the exception of the eating (comfort with food) subscale, which is expected to show less comfort around food with effective treatment. Body composition (fat and lean masses) and bone mineral density (BMD) were determined, at baseline and Week 32, by dual x-ray absorptiometry (DXA; Hologic 2000, Waltham, MA). All

DXA measurements were gathered using the same equipment and techniques. Subjects were instructed to fast for 8 hours and not to drink water or other beverages for at least 4 hours prior to DXA measurement.

Endpoints and measures of outcome

Body weight was the primary end point. Examined were the absolute change in weight, percent change in weight, and the number of subjects in each group that achieved weight losses of 5% and 10%. Secondary outcome measures included heart rate, blood pressure, frequency of adverse effects, fasting electrolytes and lipids, waist measurement, VAS-C, IWQOL, body composition and BMD.

Statistical analysis

All randomized subjects were included in the primary analysis. Putative differences between subjects in the zonisamide group versus subjects in the placebo arm were tested using Student's t-test for continuous variables and Fisher's exact test for categorical covariates. A dichotomous proxy variable denoting attrition status was also tested between groups using Fisher's exact test. Two subjects that withdrew after completing only the baseline interview were excluded from subsequent analyses.

Weight change during the study was assessed in terms of actual weight change over the six study

intervals using multivariable regression methodology, and as a dichotomous outcome of 'response,' i.e., 5% weight loss at Week 16, and 5% and 10% weight loss at Week 32. The proxy variables denoting response status were tested across treatment conditions again using Fisher's exact test. Three multivariable regression analyses were conducted. In the first, body weight at each time point was modeled using a random effects growth curve model. Heuristically, the model fits a regression line for each subject using available data points, thus maximizing use of actual data. For the second set of analyses, body weights were regressed as above with missing observations carried forward from the last recorded weight based on an intent-to-treat approach (LOCF). The final model was restricted to the subset of respondents with no missing data (completers). All models included covariates for gender and BMI as well as proxy variables denoting treatment condition, time, and a term for the interaction of treatment with time; age race, and percent body fat at baseline were not significantly associated with weight loss and, hence, excluded from the above models.

Secondary analyses were conducted over three general areas of interest. In each case, analyses were based on 2X2 repeated measures ANOVAs that included time, drug condition, and their interaction (time-by-drug). The primary interest in each instance was to

determine if subjects in the zonisamide condition were differentially affected relative to controls as operationally determined by testing the significance of the estimated interaction term. Tests in first area of interest focused on clinical indicators including levels of creatinine, glucose, triglycerides, high and low density lipoproteins (all assessed at baseline and study conclusion), waist measurements (baseline, Week 8 and Week 16), blood pressure (systolic and diastolic), and heart rate. The second general area of sampled quality of life indicators including activities of daily living, appetite, esteem, health, interpersonal relations, mobility, sex, and work using the IWQOL Scale; repeated measurements were taken at baseline, Week 8, and Week 16). The final set of secondary analyses sampled hunger and appetite using the Visual Analogue Scale for Hunger and Food Cravings. Categories sampled included sweets, breads, salts, fats, meats, sodas, and overall hunger. Measurements were sampled at baseline, Week 8, and Week 16.

The frequency of occurrence of individual adverse effect was tested across drug conditions using Fisher's exact test.

Results

Subject characteristics and disposition

Of the 68 subjects screened for participation, 8 were ineligible (Figure 1). Sixty subjects were randomized - 30 to receive zonisamide (ZON) and 30 placebo (PBO). Nine subjects - 6 in the PBO group and 3 in the ZON group - dropped out of the acute phase; thus, 51 of 60 subjects completed the first 16 weeks. The attributed reasons for premature discontinuation were: adverse events (ZON 1, PBO 2), lost to follow-up (ZON 1, PBO 2), consent withdrawn (ZON 0, PBO 2), and protocol violation (ZON 1, PBO 0).

With regard to characteristics of subjects at baseline (Table 1), there were no significant differences between the treatment groups with the following exceptions: with regard to gender distribution, there was a marginal difference ($p=0.08$) as all five men in the study were randomized to ZON. Baseline BMI was slighter lower ($p=0.07$) in the ZON group.

Table 1. Baseline Characteristics of the Subjects

Characteristic	Zonisamide (n = 30)	Placebo (n = 30)
Age, yrs	37.5 (1.3)	36.4 (1.6)
Sex, No.		
Men	5	0
Women	25	30
Race, No.		
Black	12	17
White	18	13
Weight, kg	98.2 (2.5)	97.8 (2.6)
BMI, kg/m ²	35.4 (0.7)	37.2 (0.8)
Body fat, %	40.8 (0.9)	42.6 (0.8)

Age, weight, BMI and body fat are presented as group means (SE).

BMI denotes body mass index, defined as weight in kilograms divided by the square of height in meters.

Presented first are the results of the acute phase (initial 16-week treatment), which was double-blind, and included all randomized subjects. Since the extension phase was optional and single-blind, all the important results from this phase are presented separately.

Dose

The prescribed mean highest daily dose of zonisamide was 427 (29) mg, corresponding to 4.27 capsules, whereas the placebo group received 5.00 capsules (corresponding to 500 mg).

Weight loss

Percent and absolute change in weight

The curves for weight change as a percent weight loss over the 16-week duration for zonisamide and placebo groups are shown in Figure 2 for subjects in the intent-to-treat (ITT) analysis with LOCF. The mean (SE) estimated weight loss for the zonisamide group (n=30) was 5.98% (0.82%) compared with 1.02% (0.40%) for the placebo group (n=30); time x treatment interaction was significant ($F_{1, 58} = 22.05$; $p < 0.0001$). For the ITT-LOCF population, the absolute weight changed for the zonisamide group from 98.17 (2.5) kg at baseline to 92.28 (2.47) kg at Week 16 whereas for the placebo group, the corresponding change was 97.75 (2.63) kg to 96.86 (2.78) kg (time x treatment: $F_{1, 58} = 24.65$; $p < 0.0001$). Results from random coefficient regression analyses supported differential weight loss for zonisamide-treated subjects. Regardless of imputation procedure, the drug-by-time interaction differed significantly from zero in all models. For the likelihood imputed model, the estimated regression coefficient associated with the interaction term predicted weight loss per week in excess of 0.3 kg over the course of the study; complimentary values for the other two models were 0.29 kg/wk using LOCF intent-to-treat imputation, and 0.21 kg/wk as estimated from the model based only on complete-data

subjects. Among the remaining covariates, female gender was associated with significantly lower weight levels, while higher BMI scores were associated with increasing weight levels, again irrespective of model.

For the subset of subjects completing the 16-week acute phase, the difference between treatment groups in the achieved weight loss over time was again significant ($F_{1,49} = 20.07$; $p < 0.0001$) with the ZON group losing 6.61% (0.81%) weight compared with the placebo group losing 1.30% (0.49%).

Responders ($\geq 5\%$ and $\geq 10\%$ Weight Loss)

In the ITT-LOCF population, 17 of 30 subjects (57%) in the ZON group and 3 of 30 subjects (10%) in the PBO group achieved weight loss of $\geq 5\%$ weight loss at Week 16 (Fisher's Exact; $p < 0.0003$); 7/30 ZON subjects and 0/30 PBO subjects achieved $\geq 10\%$ weight loss at Week 16 ($p < 0.0053$).

Other efficacy measures

Waist circumference decreased more in the zonisamide group over the 16 weeks (103.5 [1.6] cm to 97.2 [1.8] cm vs. 103.2 [1.9] cm to 100.5 [2.0] cm; time x treatment: $F_{1,49} = 7.75$; $p < 0.0008$). Heart rate decreased by an average of approximately 2 beats/min in the overall sample ($p < 0.0007$) although there was no difference between the groups. Systolic and diastolic blood pressure readings did not change by four months.

Safety measures

Subjects assigned to ZON reported, on average, 2.1 adverse effects (AEs) over the study period compared with 1.6 AEs for PBO ($t = -1.56$; $p < 0.125$). Of the individual AEs, 10 subjects in the ZON group and 1 in the PBO group reported fatigue (Fisher's Exact; $p < 0.006$); there were no other AEs that were reported differently by the treatment groups. Serum creatinine increased from 0.79 (0.03) mg/dL at baseline to 0.92 (0.03) mg/dL with zonisamide treatment while the change for PBO was 0.76 (0.02) mg/dL to 0.79 (0.02) mg/dL ($F_{1,49} = 14.82$; $p < 0.0003$).

Extension phase results

Of the 37 subjects (ZON 20, PBO 17) who entered the extension phase, 36 completed Week 32. One subject in the ZON group withdrew prematurely citing time constraints. Ten of 19 zonisamide subjects and none of the placebo subjects lost $\geq 10\%$ weight at Week 32 ($p < 0.0004$). Zonisamide subjects had a mean weight loss of 9.37% (1.64%) at Week 32 compared with 1.82% (0.73% for placebo subjects ($F_{1,34} = 13.02$; $p < 0.0001$)). With regard to absolute weight in kilograms, the change over the 32 weeks for the ZON group was from 96.88 (3.01) kg to 87.64 (2.95) kg contrasting with change in the placebo group from 96.39 (2.95) kg to 94.85 (3.38) kg (time x treatment: $F_{1,34} = 14.76$; $p < 0.0001$).

Waist circumference decreased more in the zonisamide group over the 32 weeks (103.5 [2.0] cm to 93.6 [2.2] cm vs. 103.8 [2.4] cm to 100.5 [2.5] cm; time x treatment: $F_{1,34} = 8.38$; $p < 0.0001$). Both treatments led to decrease in systolic blood pressure; however, the decrease was greater in the ZON group (129.1 [2.5] mmHg to 122.3 [1.8] mmHg vs. 128.2 [1.8] mmHg to 126.8 [1.8] mmHg; time x treatment: $F_{1,34} = 2.72$; $p < 0.0047$). Diastolic blood pressure decreased with ZON treatment, but not with PBO (82.5 [1.8] mmHg to 79.7 [1.2] mmHg vs. 82.5 [1.8] mmHg to 82.2 [1.1] mmHg; time x treatment: $F_{1,34} = 1.99$; $p < 0.0403$). Heart rate showed no significant change with either treatment.

Bone mineral density at lumbar vertebrae (L-BMD) did not change over time in either group. Total bone mineral density showed a small, but statistically significant ($p < 0.017$) increase in both groups although not clinically significant; there was no difference between the groups in this regard.

The following measures of the Impact of Weight on Quality of Life (IWQOL) scale improved more significantly in the zonisamide group over the placebo group at Week 32: Health ($p < 0.0030$), Work ($p < 0.0051$), Mobility ($p < 0.0019$), and Activities of Daily Living ($p < 0.0005$).

Serum creatinine increased from 0.78 (0.03) mg/dL at baseline to 0.92 (0.03) mg/dL with zonisamide

treatment while the change for PBO was 0.75 (0.02) mg/dL to 0.77 (0.02) mg/dL ($F_{1,34} = 11.01$; $p < 0.0001$). No clinically significant changes in mean lipid values were observed with either treatment although significant reductions were observed for some subjects.

Conclusion

This randomized study demonstrated that zonisamide produced a robust weight loss effect when used as an adjunct to a standard, but low-key dietary and lifestyle intervention. The drug's superior effect over placebo was demonstrated in the various analyses conducted for both the acute phase (first 16 weeks) as well as the extension phase. The difference in the weight loss efficacy between the active treatment and placebo was evident by 4 weeks and the gap widened as the study progressed. Given the low-key adjunctive dietary and lifestyle intervention provided in this study, weight loss of 9.4% at 32 weeks can be regarded a significant finding.

Reductions in certain risk factors associated with obesity were also observed. Waist circumference decreased more significantly with zonisamide therapy compared with placebo treatment, likely related to greater degree of weight loss with active treatment. There was also a meaningful reduction in systolic blood pressure although the subjects were not

hypertensive at study entry. Improvements were also noted in mobility, general health, occupational functioning, activities of daily living, reflecting an overall improved quality of life. No significant changes in mean lipid levels were observed although significant reductions were seen for some subjects.

Zonisamide was generally well tolerated. Fatigue was the only adverse effect that occurred at a higher frequency than with placebo treatment. Although not observed frequently in this study, the following adverse effects occurred frequently in the zonisamide epilepsy trials: dizziness, cognitive impairment, and somnolence. Zonisamide is a sulfonamide; there is a potential for hypersensitivity reactions. Serious hematologic events have also been reported. The risk of kidney stones also needs recognition. For the duration of treatment in this study (approximately 8 months), the rate of occurrence of kidney stones with zonisamide therapy is estimated to be 62.5 per 1000 patient-years of exposure. Consistent with data from epilepsy trials, an increase in serum creatinine was noted with zonisamide therapy, but not with placebo. Whereas the increase (approximately 16% increase) was significant, there was no further increase in the extension phase; no value exceeded the upper limit of normal range and there were no clinical events associated with the increase.

EXAMPLE 2

A 35 y.o. obese female (weight 271 lb, BMI 40 kg/m²), who failed to benefit from numerous weight loss interventions, was started on bupropion 150 mg/day and the dose was increased after 5 days to 150 mg twice a day. After one month of treatment, she lost 5 lbs, but regained 3.4 lbs during the second month - thus managing a net weight loss of 1.6 lbs after 2 months on bupropion. At this point, zonisamide was added to the regimen at 100 mg/day and the dose was increased after 2 weeks to 200 mg/day. After one month on the combination therapy, the patient had lost 11 lbs and reported no side effects. No further information is available as the patient has relocated.

EXAMPLE 3

A 47 y.o. obese female (weight 246 lb, BMI 41.4 kg/m²), who had not benefited from various treatments, was started on zonisamide 100 mg/day and the dose was increased gradually to 400 mg a day over the next 4 weeks. After one month of treatment, she lost 4.6 lbs, but there was no further weight loss during the second month. At this point, zonisamide dose was increased to 600 mg a day; the patient achieved an additional weight loss of 0.6 lb in the next month. Thus, after 3 months of zonisamide therapy, the total

weight loss with zonisamide therapy was 5.2 lb. Zonisamide was continued at the same dose and bupropion SR was started at 100 mg a day. After 10 days, the dose of bupropion was increased to 200 mg a day. One month later, the patient had lost 8.2 lbs and reported no side effects. She reported that she felt "full" after eating small portions of food, and had more energy. She had lost over 35 lbs over ten months on the combination therapy with no side effects.

EXAMPLE 4

A 46 y.o. obese female received zonisamide in a clinical trial and achieved weight loss of 35.6 lb over 32 weeks. During the 5 weeks following discontinuation of zonisamide, she gained 7.7 lb. Zonisamide was restarted, but this intervention was unsuccessful in offsetting the regained weight; after 16 weeks of therapy at doses up to 400 mg/d, the patient gained 1.2 lb. At this point, bupropion was added at 150 mg/d. After 14 weeks of combined therapy, the patient lost 9.4 lb with no adverse effects.

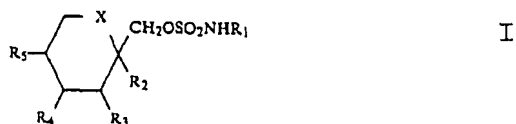
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All documents cited above are hereby incorporated in their entirety by reference.

WHAT IS CLAIMED IS:

1. A method of treating obesity in a mammal comprising administering to a mammal in need of such treatment at least one weight-loss promoting anticonvulsant and at least one compound that enhances the activity of norepinephrine and/or dopamine in amounts such that said treatment is effected.

2. The method according to claim 1 wherein said anticonvulsant is of the formula (I):



wherein X is CH₂ or oxygen,

R₁ is hydrogen or alkyl,

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl, and when X is CH₂, R₄ and R₅ can be alkene groups joined to form a benzene ring and when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together can be a methylenedioxy group of the following formula (II):

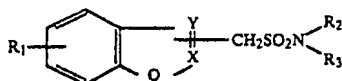


wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

3. The method according to claim 2 wherein R_1 is hydrogen or a C_1 - C_4 alkyl, straight and branched chain, and R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are a C_1 - C_3 alkyl, straight or branched chain.

4. The method according to claim 1 wherein said anticonvulsant is of the formula (III):



wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, and one of X and Y is a carbon atom and another is a nitrogen atom, provided that the group $-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof.

5. The method according to claim 1 wherein said anticonvulsant is zonisamide or topiramate.

6. The method according to claim 1 wherein said compound that enhances the activity of norepinephrine and/or dopamine effects said enhancement via uptake inhibition.

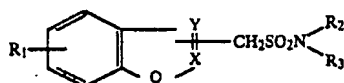
7. The method according to claim 1 wherein said compound that enhances the activity of norepinephrine and/or dopamine is bupropion, Atomoxetine or Reboxetine.

8. The method according to claim 1 wherein said anticonvulsant and said compound that enhances the activity of norepinephrine and/or dopamine are administered separately.

9. The method according to claim 1 wherein said anticonvulsant and said compound that enhances the activity of norepinephrine and/or dopamine are administered concurrently.

10. A method of reducing the risk of hypertension, diabetes or dyslipidaemia in a mammal comprising administering to a mammal in need of such reduction at least one weight-loss promoting anticonvulsant and at least one compound that enhances the activity of norepinephrine and/or dopamine in amounts such that said reduction is effected.

11. A method of treating obesity in mammal comprising administering to a mammal in need of such treatment a compound of formula (III):



wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, and one of X and Y is a carbon atom and another is a nitrogen atom, provided that the group $-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof, in an amount sufficient to effect said treatment.

12. The method according to claim 11 wherein said compound is zonisamide.

13. A composition comprising at least one weight loss-promoting anticonvulsant and at least one compound that enhances the activity of norepinephrine and/or dopamine.

14. The composition according to claim 13 wherein said compound is in dosage unit form.

15. The composition according to claim 14 wherein said composition is in the form of a tablet or capsule.

16. The composition according to claim 13 wherein said anticonvulsant is zonisamide or topiramate.

17. The composition according to claim 13 wherein said compound that enhances the activity of norepinephrine and/or dopamine is bupropion.

1/2

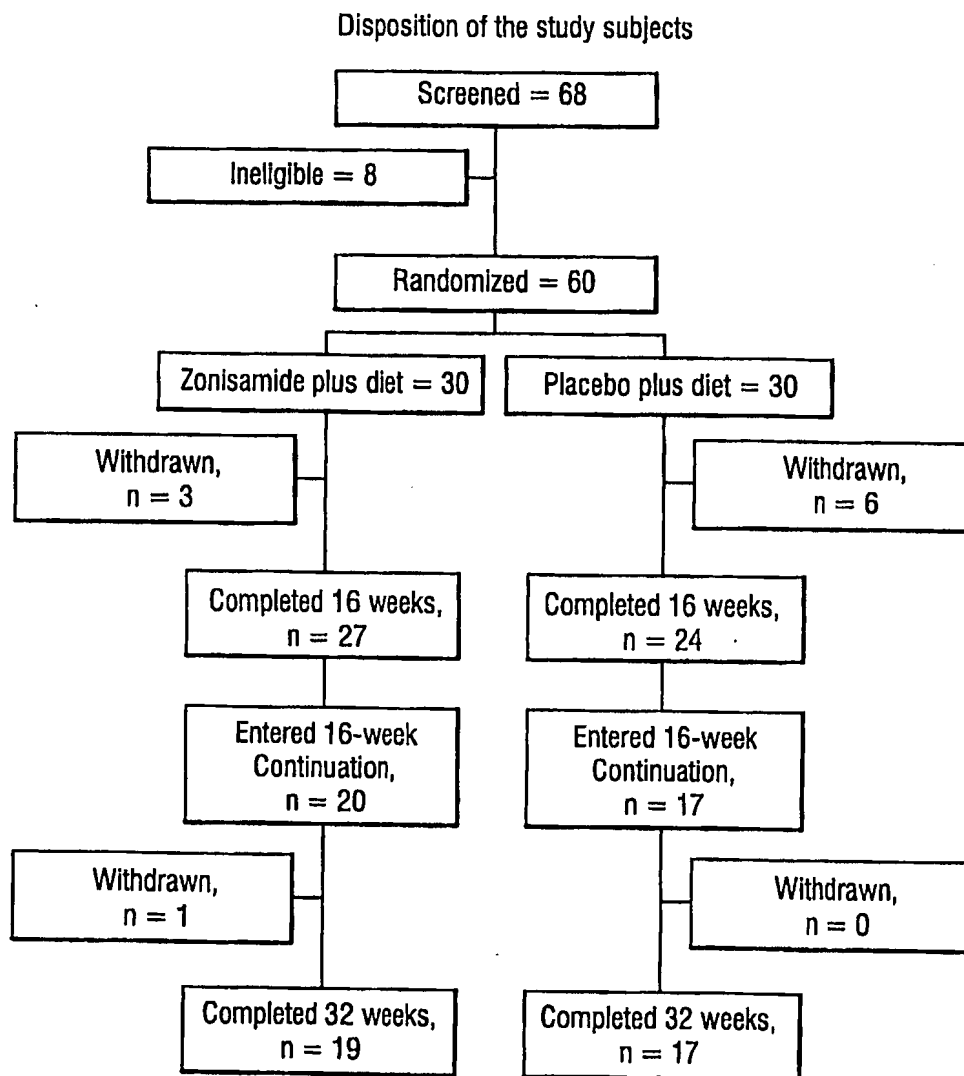
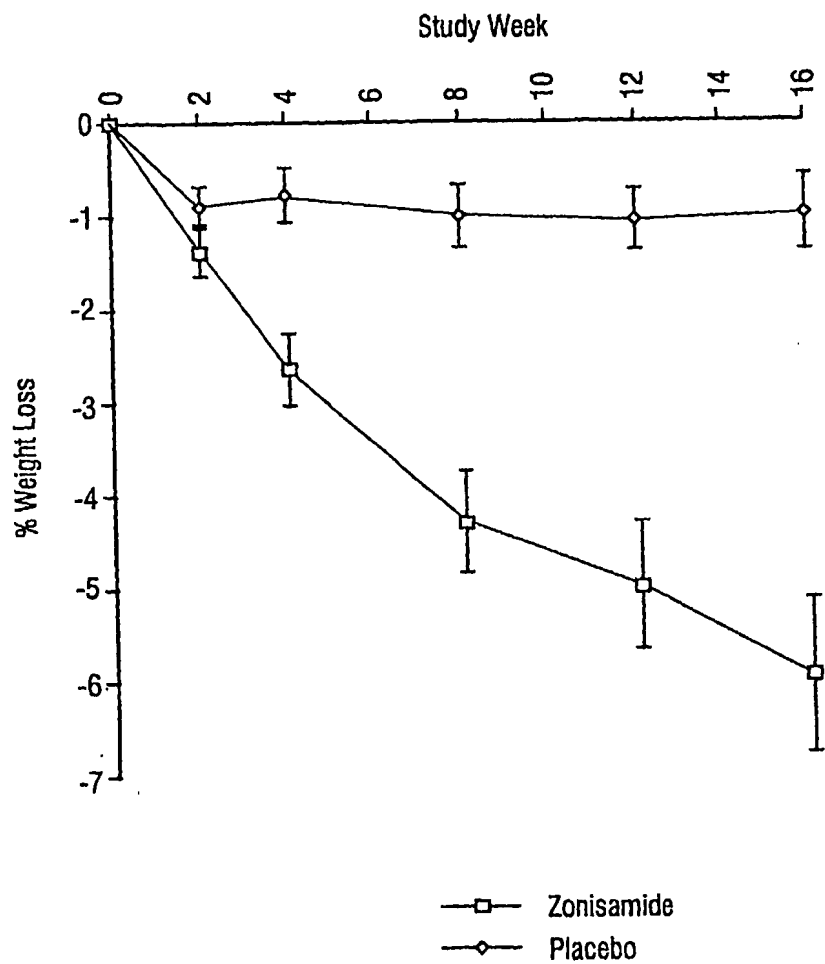


Fig. 1

2/2



Pattern of weight change from baseline to Week 16 in obese subjects who received zonisamide (n=30) or placebo (n=30). Results plotted as means (SE). Data are from the last-observation-carried-forward (LOCF) analysis.

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/15703

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : 31/42
US CL : 514/379

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/379

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database USPT on WEST, KANIOS et al, 'Compositions and methods for topical administration of pharmaceutically active agents', US-PAT-NO: 5719197, 17 February 1998, see the entire document.	1-17

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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